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# Effect of Diet or Diet Plus Physical Activity Versus Usual Care on Inflammatory Markers in Patients with Newly Diagnosed Type 2 Diabetes: The Early ACTivity In Diabetes (ACTID) Randomized, Controlled Trial

Dylan Thompson, PhD; Jean-Philippe Walhin, PhD; Alan M. Batterham, PhD; Keith A. Stokes, PhD; Ashley R. Cooper, PhD; Robert C. Andrews, MBChB, PhD

**Background**—Inflammation plays a major role in diabetes-associated cardiovascular disease (CVD). There is uncertainty whether diet and physical activity interventions can be successfully integrated into healthcare settings and reduce markers of inflammation and risk of CVD in patients with type 2 diabetes (T2D).

**Methods and Results**—Systemic markers of inflammation were determined in a 12-month, real-world, multicenter, randomized, controlled trial that investigated the effect of diet, diet plus physical activity, and usual care in 593 individuals with newly diagnosed T2D. During the first 6 months, serum C-reactive protein (CRP) improved by  $-21$  ( $-36$  to  $-1.4$ )% and  $-22$  ( $-38$  to  $-3.1$ )% in diet and diet plus physical activity arms versus usual care. There were also improvements in adiponectin and soluble intercellular adhesion molecule-1 (sICAM-1). Though medication-adjusted CRP was improved between 6 and 12 months for usual care, both interventions were more successful in reducing the relative risk of a high-risk CRP level of  $>3$  mg/L (risk ratios of 0.72 [0.55 to 0.95] for diet versus usual care and 0.67 [0.50 to 0.90] for diet plus activity versus usual care). Furthermore, sICAM-1 (a marker of vascular risk), remained substantially lower than usual care in both intervention arms at 12 months.

**Conclusions**—Motivational, unsupervised diet and/or diet plus physical activity interventions given soon after diagnosis in real-world healthcare settings improve markers of inflammation and cardiovascular risk in patients with T2D, even after accounting for the effect of adjustments to medication to try and control blood pressure, glycated hemoglobin, and lipids.

**Clinical Trial Registration**—URL: <http://www.controlled-trials.com/>. Unique identifier: ISRCTN92162869. (*J Am Heart Assoc.* 2014;3:e000828 doi: 10.1161/JAHA.114.000828)

**Key Words:** cardiovascular disease • exercise • inflammation • physical activity

Systemic markers of low-grade inflammation represent an important adjunct to the capture of conventional cardiovascular risk factors.<sup>1</sup> Of the measures that are readily available, high-sensitivity serum concentration of C-reactive protein (CRP) is the most widely used and appears to have consistent predictive value in various populations and groups. Individuals with a CRP level of greater than 3 mg/L are

considered at high risk of cardiovascular disease (CVD).<sup>1</sup> People with type 2 diabetes (T2D) tend to have higher markers of inflammation, and circulating CRP concentrations increase continuously across the spectrum of fasting glucose concentrations beginning at the lowest quartile of normal fasting glucose.<sup>2</sup> In patients with type 2 diabetes, CRP is an independent risk factor for cardiovascular events,<sup>3,4</sup> risk of death,<sup>5</sup> atherosclerotic progression,<sup>6</sup> and development of peripheral vascular disease.<sup>7</sup>

Increased physical activity and dietary advice implemented by healthcare professionals is recommended by international consensus in the management of T2D.<sup>8</sup> The effect of diet and/or physical activity on inflammation-associated cardiovascular risk in patients with T2D has been poorly characterized. Of the studies that exist, most represent small efficacy trials involving only a handful of patients and with the investment of significant resources to support lifestyle changes (eg, supervision of exercise). These small studies confirm that intensive interventions designed to reduce weight and/or increase participation in supervised exercise

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can lead to profound beneficial effects on inflammatory markers in people with T2D (eg, as reported previously<sup>9–11</sup>). One larger study confirmed that carefully supervised exercise reduces CRP in people with T2D.<sup>12</sup> However, the relevance of these findings for clinical care are uncertain, given that the provision of supervised physical activity will be unlikely in most healthcare settings because of resources that would be required. The Look AHEAD study recently demonstrated that an intensive lifestyle intervention consisting of unsupervised physical activity combined with dietary advice can reduce CRP in people with T2D.<sup>13</sup> Notably, although the exercise component in Look AHEAD was unsupervised, the clinics were weekly and the demands and resources required to roll out such an intensive intervention would still be considerable. Furthermore, it is unclear whether the diet or physical activity components of combined lifestyle interventions contribute most to an effect—which is important in order to guide the investment of limited resources.

At present, it remains unclear whether real-world physical activity and/or dietary interventions can be successfully integrated into the management of patients with T2D to improve inflammation-associated cardiovascular risk. Early ACTivity In Diabetes (ACTID) is a large study in people with T2D that was designed to evaluate the effect of physical activity over and above that of dietary intervention while controlling for overall contact time with patients.<sup>14</sup> The physical activity component of Early ACTivity In Diabetes (ACTID) was unsupervised and the intervention was designed with roll out and implementation in mind. Therefore, Early ACTivity In Diabetes (ACTID) represents a unique opportunity to investigate the effect of diet and diet plus physical activity on inflammation in a large trial in patients with T2D who are at high risk of CVD.

## Methods

### Patients

Early ACTivity In Diabetes (ACTID) was a multicenter, parallel-group, randomized, controlled trial. The study was approved by the Bath Research Ethics Committee (05/Q2001/5), and all participants provided written informed consent. This study is registered (No. ISRCTN92162869) and has been described in detail previously.<sup>14</sup>

In order to be eligible for Early ACTivity In Diabetes (ACTID), patients had to have been diagnosed with T2D within the previous 5 to 8 months and be older than 30 years at diagnosis. Exclusion criteria were age older than 80 years, glycated hemoglobin (HbA1c) concentration greater than 10%, blood pressure higher than 180/100 mm Hg, low-density lipoprotein (LDL) cholesterol concentration higher than 4 mmol/L, body-mass index lower than 25 kg/m<sup>2</sup>, mass

greater than 180 kg, use of weight-loss drugs, taking a sulphonylurea at the maximum dose, unstable angina, a myocardial infarction within the previous 3 months, inability to increase physical activity, and pregnancy or planning to become pregnant.<sup>14</sup> The study was carried out in 5 secondary care National Health Service (NHS) Trusts: Taunton and Somerset NHS Foundation Trust; North Bristol NHS Trust; Gloucestershire Hospitals NHS Trust; and Weston Area NHS Trust. Recruitment was conducted between December 2005 and September 2008.

### Recruitment and Randomization

Patients were recruited by searching the records databases of 217 general practices in southwest England. Eligible patients had been diagnosed within the previous 5 to 8 months and were older than 30 years at diagnosis. Patients were assigned using a computer-generated allocation in a 2:5:5 ratio to usual care, an intensive diet intervention, or the intensive diet intervention plus activity. Allocation was stratified by center and minimized by age, sex, fitness, route into the study, and blood pressure. Dietitians, nurses, and patients were aware of allocation, but doctors were not. All assessments were performed by nurses.

### Procedures

The usual-care arm was designed to serve as a control group and consisted of standard dietary and exercise advice after randomization, with reviews by a study doctor and nurse at baseline as well as at 6 and 12 months.

The intensive diet intervention arm aimed to enable patients to lose 5% to 10% of their initial body weight.<sup>14</sup> The diet was not prescriptive; goals were negotiated individually with each participant. Participants saw a dietitian at 3, 6, 9, and 12 months, and this contact was supplemented by dietary advice and goal setting by nine 30-minute appointments with study nurses—approximately 1 every 6 weeks over the course of the study.

Patients in the intensive diet and physical activity group received the same dietary intervention as the intensive diet group, but were also asked to undertake at least 30 minutes of brisk walking on at least 5 days per week over and above their existing physical activity. Each patient was given a pedometer (Digi-Walker CW200; Yamax, Yamasa Tokei Keiki Co., Ltd., Tokyo, Japan) and a folder containing motivating literature and pages for recording daily physical activity (pedometer readings). Activity targets were gradually increased over 5 weeks and maintained for the remainder of the study. Activity was discussed during the same nurse appointments in order to keep the total contact time the same as in the intensive diet intervention group.

## Clinical Management of Patients

Management of T2D, blood pressure, and lipid profile was undertaken by the study team for the period of the trial. Any changes in treatment of these features were made by a doctor unaware of treatment allocation and according to a strict trial protocol to keep the risk of performance bias to a minimum. Diabetes treatment was only changed in the first 6 months if fasting blood glucose concentration rose to more than 12.0 mmol/L, patients became symptomatic, or if blood pressure was higher than 160/90 mm Hg at any visit. During the second 6 months, patients were treated as appropriate to maintain the following targets: HbA1c concentration lower than 7.4%; blood pressure lower than 140/85 mm Hg; total cholesterol concentration lower than 4.0 mmol/L; high-density lipoprotein cholesterol concentration higher than 1.0 mmol/L; LDL cholesterol concentration lower than 2.0 mmol/L, and concentration of triglycerides lower than 2.0 mmol/L.

## Inflammatory Markers

Most previous studies have focused on CRP as a single marker of inflammation, but there is uncertainty regarding the extent with which CRP alone adequately captures the relevant information on future risk.<sup>15</sup> Increased hepatic secretion of CRP is generally thought to be triggered by an increase in systemic interleukin-6 (IL-6), with adipose tissue being a particularly important source of IL-6.<sup>16</sup> Increased adiposity is also associated with lower serum concentrations of adiponectin, and this adipokine has direct anti-inflammatory effects.<sup>17,18</sup> Thus, measurement of IL-6 and adiponectin provide information on pro- and anti-inflammatory pathways—which are heavily influenced by adipose tissue function. In contrast, markers such as soluble adhesion molecules provide information on inflammation within the vasculature, and such measures independently predict the risk of CVD<sup>19</sup> and stroke in people with T2D.<sup>20</sup> Thus, in the present study, we opted to measure IL-6, adiponectin, and soluble intercellular adhesion molecule-1 (sICAM-1) in addition to CRP. The vast majority of samples from Early ACTivity In Diabetes (ACTID) were available for inflammatory marker analysis, but, for logistical reasons, some samples were unavailable.

Serum CRP was determined using an automated high-sensitivity immunoturbidimetric assay and RX Daytona clinical chemistry analyzer (Randox Laboratories Ltd., Crumlin, UK). Serum was analyzed for IL-6, sICAM-1, and adiponectin using commercially available solid-phase ELISAs (Quantikine; R&D Systems Europe Ltd., Abingdon, UK). Average intra- and interassay coefficient of variation (CV) was established from the repeated analysis of 20 to 60 samples at different concentrations. The intraassay CV was 3%, 5%, 6%, and 9% for

CRP, adiponectin, sICAM-1, and IL-6, respectively. The interassay CV was 6 to 7% for all assays except IL-6, which was 16%.

## Statistical Analysis

Analysis of inflammatory outcomes at 6 months represents the effect of the interventions without the confounding complication of changes in medication, because this was unadjusted during this period. Analysis of outcomes at 12 months provides a robust comparison with usual care, because medication was adjusted to try and target predefined clinical targets (see above). Given its role in risk prediction, we examined the effect on CRP as both a continuous and dichotomized variable ( $>3$  versus  $\leq 3$  mg/L). For the continuous variable model, we applied an ANCOVA (multiple regression) model to adjust for the baseline value of CRP, the minimization variables (age, sex, fitness, route into the study, and blood pressure), and study center. Note that in the first 6 months of Early ACTivity In Diabetes (ACTID), medication was not adjusted. For the dichotomized model, we used generalized linear modeling to derive risk differences (binomial distribution with an identity link) and risk ratios (binomial distribution with a log link), adjusted for any chance imbalance between groups at baseline for the proportion of participants with a high-risk CRP value ( $>3$  mg/L). Using the risk differences, we obtained the number of participants needed to treat (with the diet plus activity or diet interventions versus usual care) for 1 additional participant to benefit ( $\text{NNT}_{\text{BENEFIT}}$ ) as  $1/\text{the absolute risk reduction}$ . Planned comparisons were conducted between diet plus activity versus usual care, diet versus usual care, and diet plus activity versus diet, with no adjustment for multiple comparisons.<sup>21</sup> The same analyses were conducted for CRP at the 12-month time point. The continuous variable analysis model was adopted for the 6- and 12-month time points for the secondary outcome variables (IL-6, sICAM-1, and adiponectin). Mean effects are presented together with their 95% confidence intervals (CIs). For the number needed to treat, a CI crossing zero implies that the intervention might have a harmful effect; in such cases, the CI was presented as extending from the number needed to treat for 1 additional participant to be harmed ( $\text{NNT}_{\text{HARM}}$ ) through infinity (absolute risk reduction of zero) to  $\text{NNT}_{\text{BENEFIT}}$ .<sup>22</sup> Continuous outcome variables were natural log transformed before analysis.<sup>23</sup> Resulting effects are therefore presented as percent (ratio) differences between arms in change from baseline, derived from back-transformation of the differences on the log scale.

Analysis of continuous outcomes was according to intention to treat using a full information maximum likelihood method<sup>24</sup> using the Stata (version 12.1; StataCorp, College Station, TX) structural equation modeling (SEM) module. For

the dichotomized CRP analysis, there was a small proportion of cases with valid outcome data, but missing baseline data; N=19 at 6 months and 17 at 12 months. These missing baselines were imputed using a valid regression method.<sup>25</sup> Both CRP and IL-6 can be influenced by acute infections, and so we used a sensitivity analysis to explore whether excluding high values (>10 or 20 mg/L for CRP and >10 pg/mL for IL-6) influenced the outcome. Excluding samples with values above these thresholds made no material difference to the results, and so the data for all available samples are presented. For the primary outcome (CRP at 6 months), we conducted exploratory analyses to examine the extent to which the intervention effects were moderated by sex, baseline CRP level (continuous), and use of statins (yes/no). Interactions between intervention arm and each of these variables were added to the statistical model. All interaction terms were entered simultaneously, rather than in separate models, to avoid potential confounding, given that baseline CRP levels were higher in women than in men and lower in those on statins versus not, and a greater proportion of men versus women were on statins. For baseline CRP level, we determined the difference in intervention effect per 2-SD

increment.<sup>26</sup> The effect of ethnicity could not be examined robustly because >95% of the sample was of white European origin. Because of the purely exploratory nature of these secondary analyses, higher-order (3-way) interactions were not examined.

For the 6-month time point, we examined the extent (expressed as a percentage) to which the total observed effects were mediated by 3 putative mechanism variables—change in body mass, change in HbA1c, and change in homeostasis model assessment of insulin resistance (HOMA-IR). This mediation analysis was conducted using the Stata software (SEM mediation module).

## Results

Of 1634 patients who were screened by telephone, 593 were enrolled into Early ACTivity In Diabetes (ACTID) and the characteristics of each group were similar at baseline (Table 1). Changes in HbA1c as well as measures of insulin resistance (HOMA-IR) and weight were greater in both intervention arms, compared to usual care, with no substantial difference between interventions.<sup>14</sup> The diet plus

**Table 1.** Summary Statistics at Baseline

	Diet (n=248)	Diet Plus Activity (n=246)	Usual Care (n=99)
Male sex N (%)	158 (64)	165 (66)	62 (63)
Age, y	60 (10)	60 (10)	60 (11)
Smoker N (%)	24 (10%)	16 (7%)	8 (8%)
White N (%)	239 (96%)	232 (94%)	96 (97%)
Median (IQR) time since diagnosis, days	186 (152 to 225)	194 (151 to 233)	185 (148 to 232)
Weight, kg	90.2 (16.7)	91.1 (16.9)	93.9 (19.0)
BMI, kg/m <sup>2</sup>	31.5 (5.7)	31.6 (5.6)	32.3 (5.9)
Diabetes medication N (%)	98 (40%)	95 (39%)	35 (35%)
Antihypertensive agents N (%)	168 (68%)	139 (57%)	58 (59%)
Lipid-lowering drugs N (%)	162 (65%)	150 (61%)	63 (64%)
HbA1c, %	6.64 (0.93)	6.69 (0.99)	6.72 (1.02)
HbA1c, mmol/mol	49 (10.2)	50 (10.8)	50 (11.1)
Systolic blood pressure, mmHg	133 (15)	133 (15)	135 (14)
Diastolic blood pressure, mmHg	79 (8)	79 (8)	80 (9)
Log HOMA-IR	1.60 (0.74)	1.65 (0.91)	1.62 (0.57)
CRP, mg/L*	2.0 (3.0)	2.0 (2.9)	2.3 (3.4)
IL-6, pg/mL*	2.0 (1.9)	2.0 (1.8)	2.4 (1.9)
sICAM-1, ng/mL*	249 (1.3)	242 (1.3)	255 (1.3)
Adiponectin, μg/mL*	5.0 (1.7)	4.8 (1.7)	5.0 (1.7)

Unless otherwise indicated, values represent means (SD). CRP indicates C-reactive protein; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; IL-6, interleukin-6; IQR, interquartile range; sICAM-1, soluble intercellular adhesion molecule-1.

\*For inflammatory variables, the mean shown is the geometric mean, and the dispersion is the SD expressed as a factor (×/÷ by).

activity group increased their mean daily step count from 6399 (3056) to 7680 (2818) and 7621 (2778) at 6 and 12 months, respectively. Approximately 90% of potential blood samples were available for assessment of CRP, IL-6, adiponectin, and sICAM-1 (Figure 1).

### Impact of Interventions on Inflammatory Markers Across Each Arm

Table 2 presents the effects of the interventions on CRP, IL-6, sICAM-1, and adiponectin for each intervention arm and analyzed as a continuous outcome. The general pattern of results at 6 months is small, but clinically meaningful, benefits of both interventions versus usual care (point estimates  $\approx 0.2$  between-subject SDs). Beneficial changes in CRP, sICAM-1, and adiponectin versus usual care were similar in both intervention arms (Table 2). The magnitude of the intervention effects in IL-6 was similar to the other markers, but the CI reveals greater uncertainty for the population effect.

Effects for CRP and adiponectin were attenuated at 12 months, but this was mainly the result of improvement in the usual-care arm (Table 2). Indeed, between 6 and 12 months, the adjusted mean values in the usual-care arm had improved by 23% for CRP and 3.2% for adiponectin. The effects on IL-6 and sICAM-1 were similar at 12 versus 6 months.

### Impact of Interventions on High-Risk CRP

The proportion of participants (SE) with a CRP  $>3$  mg/L at baseline was 44.4 (5.0)% for usual care, 37.1 (3.1)% for diet, and 35.8 (3.1)% for diet plus activity, revealing a chance imbalance. Using these baselines as a covariate in subsequent analysis of the dichotomized CRP variable (ie, high versus low-to-moderate CRP) adjusted the intervention effects appropriately to a common baseline proportion of a high-risk CRP of 37.8%.

The proportion of participants with a high-risk CRP level at 6 and 12 months is shown in Figure 2. The risk differences at 6 months were  $-3.6$  (95% CI,  $-12.2$  to  $5.1$ )% between diet and usual care,  $-10.7$  ( $-19.6$  to  $-1.7$ )% for diet plus activity versus usual care, and  $-7.1$  ( $-14.4$  to  $0.2$ )% for diet plus activity versus diet. The risk ratios for a high-risk CRP level at 6 months were 0.91 (0.72 to 1.15) for diet versus usual care, 0.72 (0.55 to 0.94) for diet plus activity versus usual care, and 0.79 (0.62 to 1.01) for diet plus activity versus diet. The number needed to treat for benefit (versus usual care) at 6 months was 28 (NNT<sub>HARM</sub> 20 to  $\infty$  to NNT<sub>BENEFIT</sub> 9) participants for the diet intervention and 10 (5 to 77) with the diet plus activity intervention.

At 12 months, the risk differences were  $-10.7$  ( $-20.0$  to  $-1.4$ )% for diet versus usual care,  $-12.6$  ( $-22.2$  to  $-3.0$ )%

for diet plus activity versus usual care, and  $-1.9$  ( $-9.5$  to  $5.6$ )% for diet plus activity versus diet. The risk ratios for a high-risk CRP level at 12 months were 0.72 (0.55 to 0.95) for diet versus usual care, 0.67 (0.50 to 0.90) for diet plus activity versus usual care, and 0.93 (0.70 to 1.24) for diet plus activity versus diet. The number needed to treat for benefit (versus usual care) at 12 months was 10 (5 to 72) participants for the diet intervention and 8 (5 to 34) with the diet plus activity intervention.

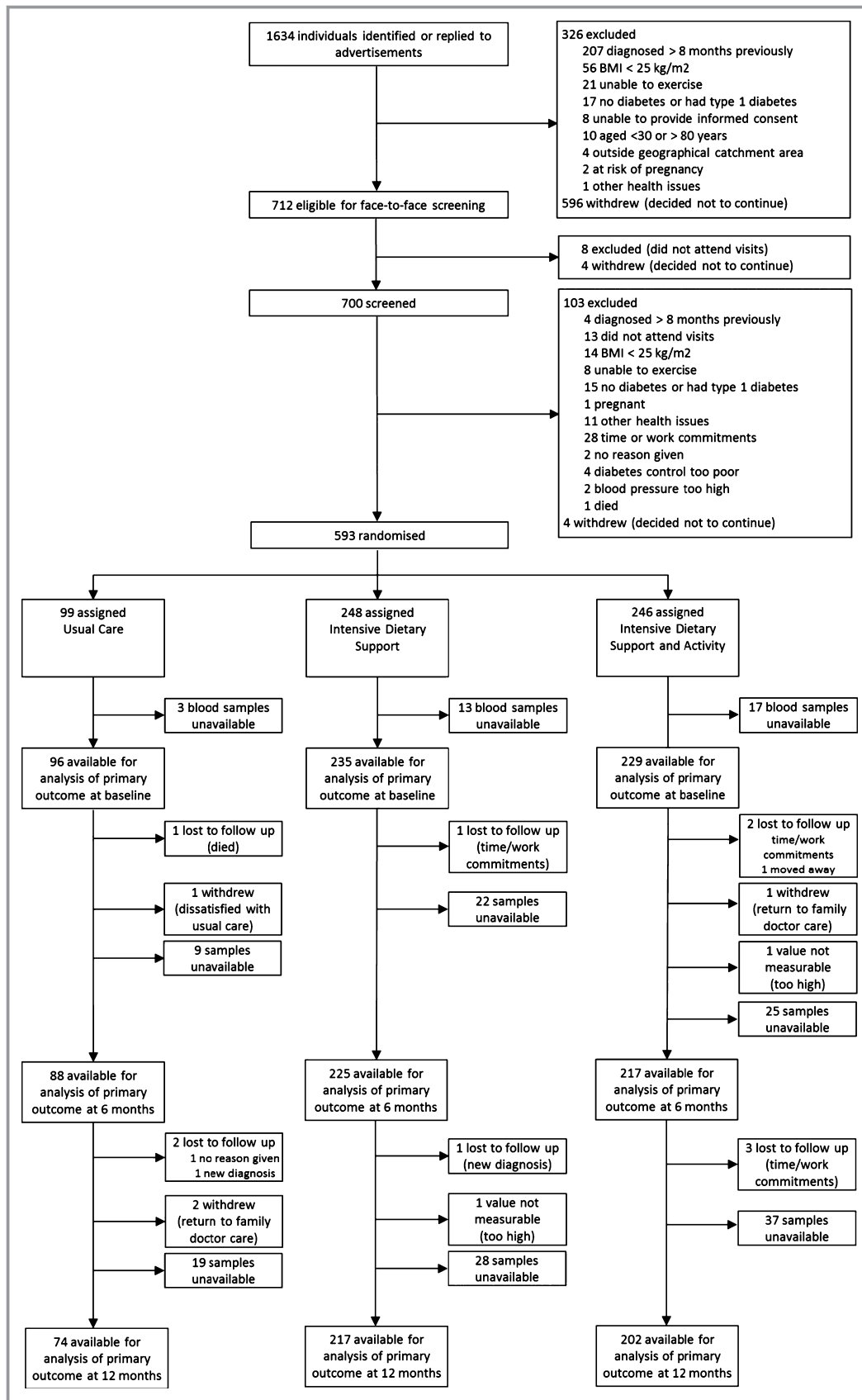
### Effect Moderation (Continuous Outcomes)

Exploratory analyses at the 6-month time point revealed a tendency for the effect of the diet plus activity intervention to be moderated substantially by sex, baseline CRP level, and statin use. Changes in CRP level (versus usual care) tended to be greater in men than women (ratio=0.66: 0.41 to 1.07), greater per 2-SD increment in baseline CRP (ratio=0.76: 0.51 to 1.12), and greater in nonusers versus users of statins (ratio=0.69: 0.44 to 1.09). Ratios less than 1 for these interaction terms indicate larger beneficial reductions in CRP from baseline versus usual care. For example, the ratio of 0.66 for the sex $\times$ diet plus activity group interaction, described above, indicates that the ratio of mean CRP at 6 months in the diet plus activity group/usual care in men is 0.66 $\times$  that in women; that is, there is a greater percent reduction in CRP in men. The evidence for effect moderation of the diet intervention was much weaker. The commensurate ratios were 0.88 (0.55 to 1.42) for male/female, 0.97 (0.66 to 1.42) per 2-SD increment in baseline CRP, and 0.84 (0.53 to 1.33) for nonusers/users of statins. Note that the 95% CIs for all interactions include the value of 1, indicating considerable uncertainty in the estimation of the true population subgroup/interaction effects.

At the 12-month time point for the diet plus activity intervention, changes in CRP level (versus usual care) tended to be larger in men than women (ratio=0.75: 0.46 to 1.22) and larger in nonusers versus users of statins (ratio=0.72: 0.46 to 1.15). Changes in CRP level were significantly greater per 2-SD increment in baseline CRP (ratio=0.61: 0.41 to 0.91). For the diet intervention, there was weaker evidence for any possible effect moderation by sex or statin use, with ratios of 1.07 (0.66 to 1.74) for male/female and 0.91 (0.57 to 1.45) for nonusers/users of statins. However, changes in CRP level were significantly larger per 2-SD increment in baseline CRP (ratio=0.67: 0.45 to 1.00).

### Mediators of Effects on Continuous Outcome Variables at 6 Months

The change in body mass mediated approximately 40% of the total effect on CRP and over half of the total effect on



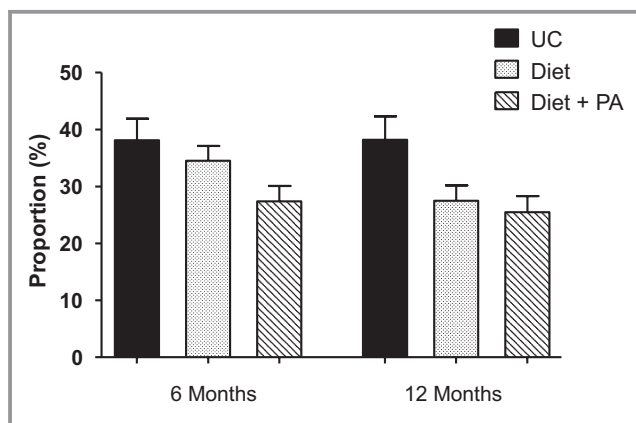
**Figure 1.** CONSORT flow diagram showing participant and blood sample availability for the current study. BMI indicates body mass index, BP, blood pressure.

**Table 2.** Adjusted Means for all Outcomes at 6 and 12 Months

Outcome		Diet	Diet Plus Activity	Usual Care	Between-Arm Difference (95% Confidence Interval)	
					6 Months	12 Months
CRP, mg/L	6 months	1.71	1.69	2.18	—	—
	12 months	1.53	1.57	1.68	—	—
Diet plus activity vs. UC					−22 (−38 to −3.4)%	−6.5 (−25 to 17)%
Diet vs. UC					−21 (−37 to −2.1)%	−9.2 (−27 to 13)%
Diet plus activity vs. diet					−1.5 (−17 to 16)%	3.1 (−12 to 21)%
IL-6 (pg/mL)	6 months	1.95	2.01	2.17	—	—
	12 months	1.85	1.94	2.14	—	—
Diet plus activity vs. UC					−7.8 (−19 to 4.4)%	−9.3 (−21 to 3.8)%
Diet vs. UC					−10 (−21 to 1.5)%	−13 (−24 to −0.9)%
Diet plus activity vs. diet					2.8 (−6.3 to 13)%	4.7 (−5.1 to 15)%
sICAM-1 (ng/mL)	6 months	234.3	233.2	247.2	—	—
	12 months	232.3	235.1	249.9	—	—
Diet plus activity vs. UC					−5.7 (−9.6 to −1.5)%	−5.9 (−10 to −1.8)%
Diet vs. UC					−5.2 (−9.1 to −1.1)%	−7.1 (−11 to −3.1)%
Diet plus activity vs. diet					−0.5 (−3.7 to 2.8)%	1.2 (−1.9 to 4.4)%
Adiponectin, $\mu$ g/mL	6 months	5.76	5.68	5.33	—	—
	12 months	5.79	5.76	5.50	—	—
Diet plus activity vs. UC					6.6 (0.8 to 13)%	4.7 (−3.4 to 13)%
Diet vs. UC					8.1 (2.3 to 14)%	5.2 (−2.8 to 14)%
Diet plus activity vs. diet					−1.4 (−5.5 to 2.8)%	−0.6 (−6.2 to 5.4)%

Geometric means are adjusted for the baseline value of the outcome, all minimization variables (age, sex, fitness, route into the study, and blood pressure), and study center. Adjusted means are expressed with additional precision to better illustrate differences between geometric means expressed as a ratio. CRP indicates C-reactive protein; IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; UC, usual care.

adiponectin (Table 3). The change in IL-6 had no substantial mediating effect for the change in CRP (data not shown).



**Figure 2.** Proportion of patients with high-risk CRP  $>3$  mg/L in usual care (UC), diet, and diet plus physical activity (PA) arms at 6 and 12 months. Proportions have been adjusted to a mean proportion at baseline of 37.8% to account for the chance imbalance between groups (see text). CRP indicates C-reactive protein.

## Discussion

Our results show that motivational unsupervised diet and diet plus physical activity interventions, integrated into healthcare settings and with relatively modest resource implications, generate beneficial changes in various inflammatory markers in early T2D. Notably, even after adjustments to medication were made to try and achieve predefined clinical targets, both interventions were better than usual care for patients with a higher risk of CVD (ie, with a CRP  $>3$  mg/L) and for measures of vascular risk (sICAM-1). There was no substantially greater benefit from adding physical activity advice to dietary advice.

At 6 months, there was a similar mean reduction in CRP in both interventions versus usual care of 21% to 22%. By 12 months, the effect on mean CRP level was substantially attenuated, but the analysis of dichotomous high-risk CRP revealed a substantial reduction in the risk of a high-risk CRP value ( $>3$  mg/L), with mean relative risk (RR) reductions of 28% for diet and 33% for diet plus physical activity and numbers needed to treat for benefit of 10 and 8 participants, respectively. As a corollary, the effect moderation analysis



**Table 3.** Mediation of Total Effects at 6 Months by 3 Putative Mechanism Variables

Outcome	Δ Body Mass	Δ Hba1c	Δ HOMA-IR
<b>CRP</b>			
Diet plus activity	40%	27%	28%
Diet	44%	22%	28%
<b>IL-6</b>			
Diet plus activity	23%	4%	8%
Diet	18%	2%	6%
<b>sICAM-1</b>			
Diet plus activity	27%	25%	29%
Diet	30%	21%	29%
<b>Adiponectin</b>			
Diet plus activity	70%	24%	42%
Diet	59%	16%	33%

The percentage shown is the mean proportion of the total effect mediated by the mechanism variable. CRP, C-reactive protein; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; sICAM-1, soluble intercellular adhesion molecule-1.

shows that the effect of both interventions is substantially greater (approximately 30% to 40% larger) in those with high-risk CRP. Importantly, although the improvements experienced by the usual-care arm attenuated the effect of both interventions on mean CRP, usual care did not successfully reduce the proportion of people with high-risk CRP (Figure 2). Hence, both interventions were more successful than usual care at substantially reducing the proportion of participants with high-risk CRP.

In the usual-care arm, mean CRP improved between 6 and 12 months once medication was adjusted to try and ensure that patients achieved predefined clinical targets. There was a greater increase in diabetes medication use in the usual-care arm between 6 and 12 months than in either intervention arm,<sup>14</sup> and diabetes medication, such as metformin, has an established effect on inflammatory markers, such as CRP.<sup>27</sup> Thus, for mean CRP at the whole-group level, conventional treatment appears to catch up with diet and diet plus physical activity advice when medication is adjusted according to fixed protocols.<sup>14</sup> However, as indicated above, this effect is not equally distributed across the sample, and, notably, the proportion of people in the usual-care arm with high-risk CRP >3 mg/L was unchanged with usual care.

Weight loss was responsible for a substantial proportion of the change in CRP in both intervention arms. Other large intensive diet and physical activity interventions found that weight loss was responsible for approximately half of the change in CRP.<sup>13</sup> Cross-sectional studies have shown that adiposity, and not differences in physical activity, explain variation in circulating markers of inflammation<sup>28,29</sup> and that

plasma adipokines are disturbed in obese, but not nonobese, patients with T2D.<sup>30</sup> Furthermore, exercise without weight loss does not change circulating concentrations of CRP.<sup>31–34</sup> Thus, although weight loss was relatively modest in both intervention arms during the first 6 months of Early ACTivity In Diabetes (ACTID), this explains much of the benefit in terms of changes in CRP and this is consistent with previous studies. The importance of weight loss for a change in CRP is interesting, and further mechanistic studies are needed to better understand the physiological processes underpinning this response.

Both interventions improved the other inflammatory markers (IL-6, sICAM-1, and adiponectin) after 6 months. As was the case for CRP, the improvement in adiponectin in the usual-care arm between 6 and 12 months meant that there were no longer any substantial differences between interventions and usual care at 12 months. This was not the case for sICAM-1, which remained different in both intervention arms when compared to usual care at 12 months. This finding for sICAM-1 is similar to the sustained changes in HbA1c, fasting insulin, and fasting glucose reported previously.<sup>14</sup> It is also noteworthy that the change in weight was a less-important mediator of the change in sICAM-1 than for CRP and adiponectin. Measurement of sICAM-1 independently predicts the risk of CVD and stroke in people with T2D.<sup>19,20</sup> Thus, these results indicate that diet and diet plus physical activity is more effective than conventional treatment at targeting inflammatory markers associated with vascular risk in patients with T2D.

There was some evidence that high-risk patients, as defined by the American Heart Association (AHA),<sup>1</sup> experienced more-rapid changes in CRP in the diet plus physical activity arm than the diet arm. The analysis of dichotomized CRP values revealed a substantial benefit only for the diet plus physical activity group after 6 months, with a mean RR reduction for high-risk CRP level (>3 mg/L) of 21% (risk ratio of 0.79) and a number needed to treat for benefit of 10 participants. However, by 12 months, physical activity had no benefit over and above that of diet in terms of (1) mean CRP, (2) proportion of patients with high-risk CRP, or (3) for any of the other inflammatory markers. The lack of additional effect from physical activity on inflammatory outcomes was surprising, but similar to that reported for other outcomes in Early ACTivity In Diabetes (ACTID), such as HbA1c.<sup>14</sup> Other studies show that *supervised* exercise alone can have a much greater effect on inflammatory markers than those reported in the present study.<sup>9–12</sup> However, Early ACTivity In Diabetes (ACTID) was a pragmatic trial designed to test the benefit from giving advice on physical activity in addition to diet in a real-world, community-based setting in the first year after diagnosis. Thus, these results show the effect from this additional advice—and not the effect of physical activity per se. This advice led to a statistically significant, but modest, increase in physical activity.<sup>14</sup> As a result of the energetics of

physical activity and other factors, such as substitution and compensation, an ostensibly large change in a given behavior might not translate into a large change in total activity energy expenditure.<sup>35</sup> Patients in the diet plus physical activity arm increased their step count by  $\approx 1300$  steps per day.<sup>14</sup> An increase in physical activity of 1300 steps per day would equate to walking  $\approx 1000$  m with an energy cost of  $\approx 50$  kcal per day.<sup>36</sup> Thus, our results show that this modest change in physical activity has no additional benefit than dietary advice on inflammatory markers and cardiovascular risk. Investing in strategies to increase physical activity further might have yielded greater improvements, but, of course, this is likely to come with a greater financial cost.

One of the strengths of Early ACTivity In Diabetes (ACTID) is that it purposefully targeted patients with newly diagnosed T2D. Another strength is that there was no change in medication over the first 6 months in order to better elucidate the effect of lifestyle intervention. Though the changes in inflammatory measures were small on average, this was accomplished with a modest change to lifestyle that was achieved without supervision, and, in particular, patients with high-risk CRP, as defined by AHA, benefited from diet and physical activity interventions.

There was an indication that the diet plus physical activity intervention might be more effective in men and in those not using statins. The latter finding is consistent with the effects on CRP observed after an intensive lifestyle intervention in which the intervention (versus control) tended to be more effective in those not on statins.<sup>37</sup>

In conclusion, these results demonstrate that motivational, unsupervised diet and diet plus physical activity interventions integrated into real-world healthcare settings generate beneficial changes in various markers of inflammation in patients with newly diagnosed T2D. Importantly, unlike usual care, both interventions reduced the proportion of patients with a high-risk CRP. Furthermore, diet and diet plus physical activity advice were more effective than usual care at improving sICAM-1, a marker of vascular risk, even when medication was used to control blood pressure, HbA1c, and lipids to agreed international targets.

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