Adiponectin and Bariatric Surgery: Associations With Diabetes and Cardiovascular Disease in the Swedish Obese Subjects Study

OBJECTIVE
Adiponectin has been implicated in the pathogenesis of type 2 diabetes, but its role for incident diabetes, myocardial infarction, or stroke in obesity is unclear. The aim of this study was to analyze the associations between systemic levels of adiponectin and the aforementioned outcomes in a population with severe obesity at high risk of diabetes and cardiovascular events.

RESEARCH DESIGN AND METHODS
We measured serum concentrations of total adiponectin in 3,299 participants of the prospective controlled Swedish Obese Subjects (SOS) Study (bariatric surgery group, n = 1,570; control group given usual care, n = 1,729). Median follow-up periods ranged between 10 and 13 years for different outcomes.

RESULTS
In models containing both baseline adiponectin and 2-year changes in adiponectin, high baseline adiponectin and 2-year increases in adiponectin were associated with decreased risk of diabetes and myocardial infarction among controls. In the surgery group, the 2-year weight loss was paralleled by substantial increase in circulating adiponectin (1,807–1,958 ng/mL per 10-kg weight loss). However, neither baseline adiponectin nor 2-year increases in adiponectin were associated with risk of diabetes or myocardial infarction in the fully adjusted models in the surgery group. No associations were found for stroke in either group.

CONCLUSIONS
Taken together, baseline adiponectin and 2-year changes were associated with incident diabetes and myocardial infarction in the control group but not in the surgery group. Baseline adiponectin did not predict treatment benefit of bariatric surgery.

DOI: 10.2337/dc13-1362

Adiponectin has anti-inflammatory, insulin-sensitizing, and atheroprotective effects in rodents (1). Although circulating concentrations of adiponectin are uniformly reduced in obesity, their clinical relevance in humans seems more complex (2). Whereas there is a consistent inverse association between circulating concentrations of adiponectin and risk for type 2 diabetes (3), associations with incident cardiovascular events are still controversial (4–6).
We and others found positive correlations of adiponectin levels with age (7), whereas few studies have investigated intraindividual changes of adiponectin over time (8,9) and their predictive value for disease outcomes (10–13). Adiponectin levels increase concomitantly with weight loss due to lifestyle intervention or bariatric surgery (10,14), but it has not been investigated in detail whether changes in adiponectin are associated with the incidence of diabetes or cardiovascular events.

The ongoing prospective controlled Swedish Obese Subjects (SOS) Study investigates the impact of bariatric surgery on morbidity and mortality in a large, nonrandomized cohort. In this study, bariatric surgery decreased the incidence of diabetes and cardiovascular events and also reduced the mortality rate compared with usual care (15–20). It is not known whether baseline concentrations and/or changes in adiponectin over time are associated with these outcomes in a population with severe obesity. Moreover, it is unclear whether changes in adiponectin simply reflect weight changes over time or whether associations between changes in adiponectin and disease risk may be independent of weight loss. The latter scenario appears conceivable because adiponectin levels are only partially explained by obesity, and other factors such as glucose tolerance, dyslipidemia, and inflammation are additional independent determinants (4,7,8). Our study therefore aimed to assess associations between baseline adiponectin levels and incident diabetes, myocardial infarction, and stroke in this severely obese population and to investigate whether changes in serum adiponectin during the first 2 years of the study are associated with the aforementioned outcomes.

RESEARCH DESIGN AND METHODS

Study Participants and Intervention
The SOS Study is an ongoing, nonrandomized, matched, prospective, controlled intervention study as described in detail previously (15–21). The study design is shown in detail in Supplementary Fig. 1. Briefly, between 1 September 1987 and 31 January 2001, a total of 4,047 obese men and women were enrolled at 25 surgical departments and 480 primary health care centers in Sweden. Subjects were included between the ages of 37 and 60 years if they had a BMI $\geq 34$ kg/m$^2$ for men and $\geq 38$ kg/m$^2$ for women. Exclusion criteria were identical for all study participants as reported before (17).

Of the individuals who were enrolled in the study, 2,010 chose bariatric surgery. These subjects underwent fixed or variable gastric banding, vertical banded gastroplasty (VBG) or gastric bypass (21). To this surgery group, 2,037 control individuals were matched contemporaneously using 18 matching variables predicted to possibly affect prognosis as described (20). The 18 variables used for matching were sex, postmenopausal status, age at exam, daily smoking, diabetes, weight, height, hip circumference, waist circumference, systolic blood pressure, triglycerides, total cholesterol, current health, monotony avoidance, psychasthenia, quality of social support, quality of social support, and stressful life events. An automated matching procedure was performed by a computer algorithm designed to minimize differences between the two treatment groups with respect to any of 18 matching variables. Hence the final matching result could not be influenced by the investigators. The control group received the nonsurgical treatment for obesity that was established at the primary health care center at which they were registered. This nonsurgical treatment was not standardized and ranged from sophisticated lifestyle intervention and behavior modification to, in some practices, no treatment whatsoever. The study was approved by seven regional ethics review boards in Sweden. All patients gave informed consent to participate in the study. The study is registered at clinicaltrials.gov (NCT0147952).

The current study is explorative, and all analyses were carried out per protocol, i.e., initial controls who underwent bariatric surgery during the follow-up ($n = 121$) and patients in the surgery group who underwent a second bariatric surgery resulting in a change of the original surgery group ($n = 307$) were excluded, which reduced the sample size to $n = 1,916$ and 1,703 in the control and surgery group, respectively (total $n = 3,619$).

Outcome Measures
The primary outcome of the SOS Study was overall mortality, and secondary outcome variables included diabetes and cardiovascular events. All participants were examined at matching and baseline examinations and after $0.5$, $1$, $2$, $3$, $4$, $6$, $8$, $10$, $15$, and $20$ years. Blood samples were taken at matching and baseline examinations as well as after $2$, $10$, $15$, and $20$ years. The baseline questionnaire included items on previous diagnosis of diabetes, myocardial infarction, and stroke. The schedule, questionnaires, physical examinations, and laboratory measurements were identical for both groups.

We considered a participant to have type 2 diabetes if he or she reported the use of diabetes medication or if there was documentation of a fasting venous whole-blood glucose level of 110 mg/dL (6.1 mmol/L) or higher (measured until 2009). If fasting venous plasma glucose was measured instead (after 2009), the cutoff value for a diagnosis of diabetes was 126 mg/dL (7.0 mmol/L) or higher (18).

Cardiovascular events were defined as incident fatal and nonfatal myocardial infarction or incident stroke, whichever occurred first. As described previously (17), the following ICD-9/International Statistical Classification of Diseases, Tenth Revision, codes were used: codes $410/121$, $I22$ for myocardial infarction and codes $431/161$ (intracerebral bleeding); $433; 434/I63, I65, I66$ (intracerebral artery occlusion); and $436/164$ (acute but nondefined stroke in terms of bleeding or occlusion) for stroke. Angina pectoris, claudication, transitory ischemic attacks and subarachnoidal bleeding were not included in our outcome variables. Incident cases were identified by cross checking the SOS database against the Swedish National Patient Register, the Cause of Death Registry, and the Registry of the Total Population. Median duration of follow-up for incident diabetes, cardiovascular...
events, myocardial infarction, and stroke was 10, 13, 13, and 13 years, respectively.

**Laboratory Measurements**

Serum concentrations of total adiponectin were determined using the Quantikine ELISA kit from R&D Systems (Wiesbaden, Germany). Serum samples were from examinations at study baseline and at follow-up after 2 and 10 years using identical standard operating procedures for blood collection, processing, and storage. All blood samples were obtained in the morning after a 10–12-h fast. Sufficient baseline serum samples were not available for 187 controls and 133 individuals in the surgery group, so serum adiponectin was measured for 3,299 participants at baseline. In addition, serum samples were available from 2,886 participants after 2 years and from 2,312 participants after 10 years. Adiponectin measurements were performed consecutively in the same laboratory (German Diabetes Center). Mean intra-assay and interassay coefficients of variation were 3 and 13%, respectively. The limit of detection was 3.9 ng/mL. All samples gave values above the limit of detection. C-reactive protein (CRP) was measured with an ultrasensitive immunoturbidimetric method (Sentinel, Milan, Italy) using the Architect c8200 analyzer (Abbott Laboratories, Abbott Park, IL). Urinary albumin excretion was calculated based on 24-h urine collection, according to the formula: [urine albumin concentration (mg/L) * urine volume (L)] / urine collection time (min), and expressed as milligrams per 24 h.

**Statistical Analyses**

Mean values and SDs (or proportions) were used to describe the baseline characteristics of the study population stratified into treatment groups or according to the incidence of outcomes. Student t test, ANCOVA, and Fisher’s exact test were used to test for differences between groups. Individuals with prevalent diabetes were excluded for the analysis of diabetes incidence. Associations between changes in adiponectin and changes in body weight were assessed by linear regression analysis, and an interaction test was used to test for differences in the strength of the association between the different treatment groups. Hazard ratios (HRs) and corresponding 95% CIs for the association between baseline adiponectin or 2-year changes in adiponectin were calculated with Cox proportional hazard regression models and standardized to 1,000 ng/mL of the respective value. Individuals with incident events before the 2-year follow-up examination were excluded when 2-year changes in adiponectin were analyzed with regard to the respective outcome. The interaction between adiponectin and sex was analyzed for each outcome, but no significant interaction was observed, so analyses were performed for men and women combined. All P values are two-sided. Statistical analyses were performed using the Stata statistical package version 10.1 (StataCorp LP, College Station, TX).

**RESULTS**

**Cohort Description**

Baseline characteristics of the 3,299 SOS Study participants for whom samples were available for adiponectin measurements are given in Table 1. Briefly, individuals in the surgery group were slightly younger and heavier and had slightly less favorable metabolic risk factors than individuals in the control group. Supplementary Tables 1 and 2 show that the group of individuals for whom baseline or 2-year data for adiponectin were lacking was comparable to the rest of the cohort, although individuals without data for adiponectin were more likely to be female in both control and surgery groups.

During follow-up, there were 487 incident cases of diabetes (380 and 107 in the control and surgery group, respectively), 278 (155/123) incident cardiovascular events (myocardial infarction or stroke, whichever came first), 169 (91/78) incident cases of myocardial infarction, and 128 (72/56) incident cases of stroke (Table 2). Median follow-up periods ranged between 10 and 13 years. Supplementary Tables 1–6 show the baseline characteristics of the study population stratified by all four outcomes for each treatment group.

**Adiponectin Levels at Baseline**

At baseline, mean serum adiponectin was 8,268 (SD 4,886) ng/mL in the control group and 7,470 (SD 4,178) ng/mL in the surgery group (P < 0.001) (Table 1). In the conventionally treated control group, individuals who suffered from incident diabetes, cardiovascular events, or myocardial infarction during the follow-up period had lower serum adiponectin levels at baseline compared with individuals that remained free from these diseases (Table 2). No differences in baseline serum adiponectin levels were found for individuals with or without incident stroke (Table 2). In the surgery group, individuals with incident diabetes had lower baseline adiponectin levels than those who remained free from diabetes during follow-up, while no there were no differences in baseline adiponectin in individuals with and without cardiovascular events (Table 2).

**Associations Between Baseline Adiponectin and Incident Diabetes**

High baseline adiponectin levels were associated with decreased incidence of diabetes in both the control group (HR [95% CI] for 1,000 ng/mL of adiponectin 0.911 [0.879–0.943]) and in the surgery group (HR 0.907 [0.852–0.966]) after adjustment for sex, age, and BMI (Table 3, model 1). After adjustment for additional baseline confounders, including lipids, lipid-lowering medication, blood pressure, antihypertensive medication, glucose, insulin, CRP (as proinflammatory immune marker), impaired kidney function (assessed by urinary albumin excretion), and sleep apnea (both comorbidities of obesity) (Table 3, model 3), high baseline serum adiponectin remained associated with lower diabetes risk in the control group (HR [95% CI] for 1,000 ng/mL of adiponectin 0.949 [0.915–0.985]). In the surgery group, which had a much smaller number of cases than the control group, the effect estimate was rather similar but only borderline significant due to a wider 95% CI (0.935 [0.874–1.000]).

**Associations Between Baseline Adiponectin and Cardiovascular Disease**

In the control group, high baseline adiponectin levels were associated with
decreased risk for cardiovascular events and myocardial infarction after adjustment for sex, age, and BMI (Table 3, model 1), but after adjustment for additional confounders, the associations were attenuated to nonsignificance (Table 3, model 2). In the surgery group, there were no significant associations between baseline adiponectin and cardiovascular events. Additional adjustment for high-sensitivity CRP, kidney function, and sleep apnea had virtually no impact on HRs (Table 3, model 3).

### Baseline Adiponectin and Treatment Benefit
We found no interaction between baseline adiponectin levels and treatment group with respect to incidence of diabetes ($P$ for interaction 0.787) or cardiovascular events ($P$ for interaction 0.268). In other words, the strengths of the associations between adiponectin and risk of diabetes (or cardiovascular events) did not differ significantly between surgery and control groups.

### Changes in Adiponectin and Body Weight During Follow-Up
Mean adiponectin levels increased by 4,877 ng/mL ($P < 0.001$) in the surgery group during the first 2 years of follow-up parallel to a loss of 23.7% of body weight.
adiponectin levels were less pronounced by adjustment for baseline age, sex, and BMI, and adiponectin levels (data not shown). These results were not affected by adjustment for multiple confounders, including baseline adiponectin levels (HR [95% CI] 0.844 [0.798–0.894] and 0.913 [0.842–0.990], respectively) (Table 4, model 3). Again, adjustment for CRP, kidney function, and sleep apnea as comorbidities of obesity had only a minor influence on the observed effect sizes (model 4).

Where additional adjustment for changes in BMI (model 5) abolished the association in the surgery group, the HR was almost unchanged in the control group.

Two-year increases in adiponectin were also associated with lower risk of myocardial infarction among controls after adjustment for multiple confounders, including baseline adiponectin. This risk reduction was independent of BMI changes. There were no associations between 2-year changes in adiponectin and the incidence of cardiovascular events or stroke in either treatment group (Table 4).

When 2-year changes in adiponectin were included in the analysis of baseline adiponectin levels in relation to incident outcomes (Table 3, model 4), the associations between high serum adiponectin levels at baseline and reduced risk of diabetes remained significant in the control group (HR [95% CI] 0.904 [0.868–0.942]), and the association between high adiponectin and reduced risk of myocardial infarction was strengthened in controls (HR [95% CI] 0.891 [0.812–0.971]) compared with model 3. In contrast, inclusion of 2-year adiponectin changes did not affect the nonsignificant associations between adiponectin and outcomes in the surgery group (Table 3, model 4).

In a sensitivity analysis, we recalculated all models presented in Tables 3 and 4, substituting BMI with waist circumference as measure of abdominal obesity, and found that HRs were virtually unchanged (data not shown).

**CONCLUSIONS**

In this study we show that in models containing baseline adiponectin and 2-year changes in adiponectin, high serum adiponectin and its 2-year increases were associated with reduced...
risk for diabetes and myocardial infarction in the control group (i.e., obese patients given usual care). For stroke, there were no significant associations with baseline adiponectin or its changes after adjustment for multiple confounders. Furthermore, baseline adiponectin was not a predictor of the treatment benefit of bariatric surgery in terms of effects on incidence of diabetes and cardiovascular events during follow-up.

In the surgery group, body weight decreased and serum adiponectin increased markedly. Two-year increases in adiponectin were associated with decreased risk of diabetes, but this association was fully explained by weight changes in the surgery group. No associations were found between baseline adiponectin, its 2-year changes, and incident cardiovascular events in the fully adjusted models.

Associations between adiponectin levels and cardiometabolic outcomes have not been investigated in a large severely obese population before. This is important, as these associations appear to differ between populations (e.g., general population, individuals with preexisting cardiovascular disease, inflammatory conditions). In addition, our study also investigates the relationship between weight changes, changes in adiponectin levels, and disease incidence in a conventionally treated obese patient group and a group of obese patients with surgically induced weight loss.

### Table 4—Association between 2-year changes in adiponectin and incidence of diabetes, cardiovascular events, myocardial infarction, and stroke

<table>
<thead>
<tr>
<th>Outcome/treatment group</th>
<th>Events/number at risk</th>
<th>Model 1 HR</th>
<th>95% CI</th>
<th>Model 2 HR</th>
<th>95% CI</th>
<th>Model 3 HR</th>
<th>95% CI</th>
<th>Model 4 HR</th>
<th>95% CI</th>
<th>Model 5 HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td><strong>Diabetes</strong></td>
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<tr>
<td>Control</td>
<td>363/1,262</td>
<td>0.851</td>
<td>0.807–0.897</td>
<td>0.844</td>
<td>0.801–0.890</td>
<td>0.844</td>
<td>0.798–0.894</td>
<td>0.840</td>
<td>0.793–0.890</td>
<td>0.861</td>
<td>0.808–0.916</td>
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<tr>
<td>Surgery</td>
<td>105/1,186</td>
<td>0.913</td>
<td>0.846–0.985</td>
<td>0.914</td>
<td>0.844–0.989</td>
<td>0.913</td>
<td>0.842–0.990</td>
<td>0.919</td>
<td>0.846–0.997</td>
<td>1.014</td>
<td>0.908–1.133</td>
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<tr>
<td><strong>Cardiovascular event</strong></td>
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<tr>
<td>Control</td>
<td>118/1,406</td>
<td>0.926</td>
<td>0.842–1.019</td>
<td>0.939</td>
<td>0.853–1.035</td>
<td>0.954</td>
<td>0.887–1.026</td>
<td>0.957</td>
<td>0.891–1.028</td>
<td>0.961</td>
<td>0.891–1.038</td>
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<tr>
<td>Surgery</td>
<td>110/1,410</td>
<td>0.978</td>
<td>0.937–1.020</td>
<td>0.991</td>
<td>0.951–1.034</td>
<td>0.988</td>
<td>0.950–1.029</td>
<td>0.987</td>
<td>0.948–1.027</td>
<td>1.000</td>
<td>0.952–1.051</td>
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<tr>
<td><strong>Myocardial infarction</strong></td>
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<tr>
<td>Control</td>
<td>69/1,408</td>
<td>0.839</td>
<td>0.715–0.986</td>
<td>0.860</td>
<td>0.731–1.013</td>
<td>0.852</td>
<td>0.745–0.973</td>
<td>0.860</td>
<td>0.757–0.977</td>
<td>0.858</td>
<td>0.750–0.981</td>
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<td>Surgery</td>
<td>69/1,410</td>
<td>0.982</td>
<td>0.933–1.033</td>
<td>0.997</td>
<td>0.949–1.048</td>
<td>1.002</td>
<td>0.954–1.052</td>
<td>1.003</td>
<td>0.955–1.054</td>
<td>1.013</td>
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<tr>
<td><strong>Stroke</strong></td>
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<tr>
<td>Control</td>
<td>56/1,413</td>
<td>1.018</td>
<td>0.922–1.123</td>
<td>1.028</td>
<td>0.923–1.144</td>
<td>1.036</td>
<td>0.938–1.144</td>
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<td>0.935–1.139</td>
<td>1.038</td>
<td>0.933–1.154</td>
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<tr>
<td>Surgery</td>
<td>51/1,412</td>
<td>0.986</td>
<td>0.927–1.050</td>
<td>0.997</td>
<td>0.936–1.062</td>
<td>0.977</td>
<td>0.924–1.034</td>
<td>0.973</td>
<td>0.918–1.032</td>
<td>1.003</td>
<td>0.938–1.071</td>
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</tbody>
</table>

HRs are from Cox proportional hazards models. Individuals with incident events before the 2-year follow-up examination were excluded. HRs are given per 1,000 ng/mL of 2-year change of adiponectin. Sds for 2-year changes in adiponectin for the control and surgery groups were 2,635 and 5,418 ng/mL, respectively. Model 1 is adjusted for baseline adiponectin. Model 2 is model 1 + sex, age, and BMI at baseline. Model 3 is model 1 + total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, alcohol consumption, smoking, use of blood-pressure-lowering medication at baseline, baseline adiponectin, and a) blood glucose and serum insulin at baseline for incidence of diabetes or b) diabetes status at baseline for the other end points. Model 4 is model 3 + CRP, urinary albumin excretion, and sleep apnea (self-reported). Model 5 is model 4 + 2-year changes in BMI.
than in the control group given usual care. Although the direct comparison of effect sizes between surgery and control groups in the SOS Study is complicated by the different ranges of weight changes, the data suggest that the increase in circulating adiponectin after surgery may partly be mediated by mechanisms independent of the prevailing weight loss. In our control group, the association between changes in serum adiponectin and weight changes was similar to that observed in the lifestyle group of the Diabetes Prevention Program (DPP; +500 ng/mL per 5-kg weight loss over 1 year) but higher than in the DPP control group (+300 ng/mL) (10). This difference can result from higher baseline BMI—and thus lower adiponectin levels—in the SOS Study compared with the DPP.

Adiponectin and Incident Diabetes
Whereas previous studies investigated associations between baseline adiponectin and outcomes such as diabetes (24), we also examined whether associations between baseline adiponectin and changes in adiponectin with various outcomes can be explained by baseline BMI and BMI changes. We found that high baseline adiponectin was associated with reduced risk of diabetes. Thus we show that the inverse association between baseline adiponectin and incident diabetes is also present in a cohort with severe obesity, whereas previous cohort studies focused on considerably less obese individuals (24). Moreover, increases in adiponectin were also associated with lower risk of diabetes among controls. Importantly, both associations were independent of each other and remained significant even after extensive adjustment, which included baseline BMI and 2-year changes in BMI. One-year changes in adiponectin and weight have been examined in the aforementioned DPP (10). In the DPP, incident diabetes was more strongly associated with baseline adiponectin levels than with 1-year changes in adiponectin after adjustment for baseline weight and 1-year weight changes. The SOS cohort differed from the DPP cohort by higher degree of obesity, larger weight loss in the surgery group, less ethnic heterogeneity, and longer follow-up. We can therefore not exclude that our finding that upregulation of adiponectin is independently associated with lower risk of diabetes is specific for an obese cohort and may not be generalizable to less obese individuals.

In the surgery group, the association between baseline levels of circulating adiponectin and diabetes risk was not significant after adjustment for multiple confounders (model 3, HR [95% CI] 0.935 [0.874–1.000]), but the HR was comparable to the control group, and the difference in statistical power caused by the lower number of cases in the surgery group most likely contributed to this result. We are not aware of any other study that investigated associations of adiponectin changes after bariatric surgery on clinical outcomes. Moreover, baseline adiponectin levels did not modify the benefit of bariatric surgery with respect to the incidence of diabetes and can therefore not be used to improve the selection of candidates for bariatric surgery if the aim is to prevent diabetes.

Adiponectin, Myocardial Infarction, and Stroke
Inverse associations between adiponectin and cardiovascular risk would be biologically plausible because adiponectin has been shown to decrease the expression of adhesion molecules on endothelial cells, thereby reducing monocyte attachment; to activate endothelial nitric oxide synthase; to stimulate endothelial cell migration, differentiation, and survival; and, finally, to diminish the formation of atherosclerotic lesions (1). The divergent data in the literature regarding whether or not adiponectin is a cardioprotective adipokine may, in part, be due to differences in outcome definitions, which may or may not include cardiovascular mortality, myocardial infarction, stroke, angina, and revascularization with percutaneous coronary intervention or coronary artery bypass grafting. It has been suggested that associations between adiponectin and cardiovascular disease depend on the outcomes that are included in the analysis (25), and this is supported by our data from the SOS Study, which indicate that myocardial infarction and stroke should be analyzed separately. If only studies that have a similar outcome based on fatal and nonfatal myocardial infarction are considered, the direction of association correlates with the stage of cardiovascular disease at study baseline: on the one hand, usually no (26–28) and, less frequently, inverse (29) associations with risk of myocardial infarction predominate in cohorts that were population based and/or mostly without preexisting cardiovascular disease at baseline (30). On the other hand, positive associations were found mainly (31–33), albeit not exclusively (34), in individuals with a history of cardiovascular disease. The latter finding may be explained as “reverse epidemiology” in which upregulated adiponectin concentrations represent a compensatory mechanism to counteract metabolic, vascular, and proinflammatory stress (4,5). This explanation is more likely than the alternative that adiponectin directly damages the vasculature. Although animal models and preclinical studies are conflicting regarding whether or not adiponectin contributes to lower cardiovascular risk (1,35), there are no data that adiponectin can actually increase this risk.

Against this background, our data are novel because they provide first estimates for associations between adiponectin and cardiovascular outcomes in a large obese cohort (i.e., in a cohort with relatively low baseline adiponectin levels) and also include adiponectin changes. We show that high baseline adiponectin and increases in adiponectin are both independently associated with low risk of myocardial infarction among the control individuals without surgical intervention when both variables are included in the same model. These associations are not explained by baseline BMI or BMI changes, and we do not find evidence of “reverse epidemiology” in this group of individuals.

In contrast, there was no association with the risk of stroke. This supports the notion that there is only a partial overlap in inflammation-related risk factors for both conditions and that adiponectin has no protective effects...
against cerebrovascular events. The findings of the SOS cohort on stroke are in line with the majority of previous prospective studies in leaner cohorts that also revealed no association between adiponectin and incidence of stroke after adjustment for confounders (12,30,36–38). However, it should be noted that stroke can be ischemic or hemorrhagic, and the type of stroke was not defined in our study. One recent study reported that higher baseline adiponectin was associated with higher risk of ischemic stroke in men (39), and we cannot exclude that associations between adiponectin and stroke may depend on the type of stroke. In contrast with the control group, there was no evidence for associations between circulating adiponectin, myocardial infarction, and stroke in the surgery group. We have shown before that higher plasma insulin at baseline was related to the effectiveness of surgery in the prevention of cardiovascular events (17), but this was not the case for adiponectin levels at baseline in the current study. However, additional studies are needed to identify biomarkers at baseline that are associated with health outcomes of bariatric surgery and thus help identify individuals who benefit most from this intervention and others for whom nonsurgical treatment may be preferable.

Strengths and Limitations
The main strengths of the current study are the large size of the cohort, the long follow-up, and the opportunity to investigate associations between adiponectin and various outcomes in severely obese individuals without and with bariatric surgery as intervention. The main limitation of the SOS Study is that it was not randomized. However, this should not affect the estimates of associations between adiponectin and outcomes within each group. In addition, the SOS Study included white middle-aged obese men and women from Sweden, so our data may be generalizable to comparable populations in Europe or North America but not necessarily to populations with different ethnic backgrounds or different age ranges. Another limitation of our study is that the diabetes follow-up did not include oral glucose tolerance tests or HbA1c measurements, and some individuals may therefore have been misclassified. No autoantibodies were determined to exclude cases of type 1 diabetes or latent autoimmune diabetes in the adult, but based on the age of onset and risk factor profile, it can be assumed that the vast majority of patients with incident diabetes have type 2 diabetes. We only measured total adiponectin and not its different isoforms. However, recent studies indicate that total adiponectin and high-molecular-weight adiponectin are closely correlated and that their associations with incident diabetes or cardiovascular events are rather similar (28,40). Finally, it should also be noted that the statistical power to reveal associations differed by outcome, as we had more cases for incident diabetes in both groups compared with incident myocardial infarctions and strokes.

In conclusion, bariatric surgery led to a substantial increase in circulating adiponectin in the SOS Study irrespective of the type of surgery. We show for the first time in a large obese population that baseline adiponectin concentrations and their changes over 2 years were inversely associated with risk of diabetes and myocardial infarction in the control group independently of each other and independently of weight changes. In contrast, these associations were not significant in the surgery group. Neither baseline adiponectin nor its 2-year changes were associated with risk of stroke in either group. Baseline levels of adiponectin were not associated with the impact of bariatric surgery on any of the outcomes investigated here and can therefore not be used as predictor of treatment benefit.

Acknowledgments. The authors thank the staff members from the 25 surgical departments and 480 primary health care centers in Sweden that participated in the study. The authors acknowledge Gerd Bergmark for invaluable administrative support in the SOS Study and Ingrid Vinsa for excellent technical assistance (both from Sahlgrenska Academy). The authors thank Gabi Gornitzka, Ulrike Poschen, and Karin Röhrig (German Diabetes Center) for their excellent technical assistance.

Funding. This study was supported by grants from the Swedish Research Council (K2010-55X-11285-13), the Swedish Foundation for Strategic Research to the Sahlgrenska Centre for Cardiovascular and Metabolic Research, the Research Foundation of the Swedish Diabetes Association (Diabetesfonden), and the Swedish federal government under the LUA/ALF agreement (L.S.). The German Diabetes Center is funded by the German Federal Ministry of Health and the Ministry of Innovation, Science, and Research of the State of North-Rhine-Westphalia. This study was supported in part by a grant from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. C.H. helped design the overall study, obtained funding, supervised laboratory measurements, helped plan statistical analyses, contributed to discussion, and wrote the manuscript. M.P. helped design the overall study, performed statistical analyses, contributed to discussion, and edited the manuscript. P.A.S. helped design the overall study, contributed clinical data used in this study, helped plan statistical analyses, contributed to discussion, and edited the manuscript. M.C. acquired laboratory data used in this study, contributed to discussion, and edited the manuscript. M.R. contributed clinical data used in this study, contributed discussion and edited the manuscript. L.S. initiated the SOS Study, contributed clinical data used in this study, helped plan statistical analyses, contributed to discussion, and edited the manuscript. L.C. helped design the overall study, contributed clinical data used in this study, helped plan statistical analyses, contributed to discussion, and edited the manuscript. P.J. contributed clinical data used in this study, contributed discussion, and edited the manuscript. M.R. contributed to discussion and edited the manuscript. L.S. initiated the SOS Study, contributed clinical data used in this study, helped plan statistical analyses, contributed to discussion, and edited the manuscript. L.C. helped design the overall study, contributed clinical data used in this study, helped plan statistical analyses, contributed to discussion, and edited the manuscript. All authors approved the final version. M.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Data from this study were presented at the joint Scientific Sessions of the Councils on Epidemiology and Prevention and Nutrition, Physical Activity, and Metabolism of the American Heart Association, San Diego, CA, 13–16 March 2012.

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